

## Histopathology of parasellar neoplasms

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# Histopathology of Parasellar Neoplasms

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## Keywords

Parasellar region · Neoplasms · Histopathology

## Abstract

The anatomical and histological complexity of the parasellar region as well as the presence of embryonic remnants determine the huge diversity of parasellar neoplasms. Some of them are only located in the parasellar region, whereas others can occur elsewhere, within or outside the central nervous system. Their spectrum ranges from histologically benign and low-grade malignant to high-grade malignant tumours. Although rare, metastases can pose differential diagnostic dilemmas. The severity of the clinical picture, the challenges of surgery and the risk of adverse sequelae related to surgery or radiotherapy make parasellar tumours interesting entities for the clinicians irrespective of their histological malignancy grade. Due to the different cell origins of parasellar tumours, the World Health Organization classification system does not categorise them as a distinct group. Detailed criteria for classification and malignancy grading are presented in the classification systems covering central nervous system tumours, haematological malignancies and

tumours of the soft tissue and bone. In the last few years, molecular genetic features have been integrated into the diagnosis of several types of the parasellar tumours enhancing diagnostic accuracy and providing information of the value for targeting therapies. In this review, we will present histopathological and molecular genetic features, updated classification criteria and recent advances in the diagnostics and rationale for novel pharmacological therapies of selected types of parasellar neoplasms.

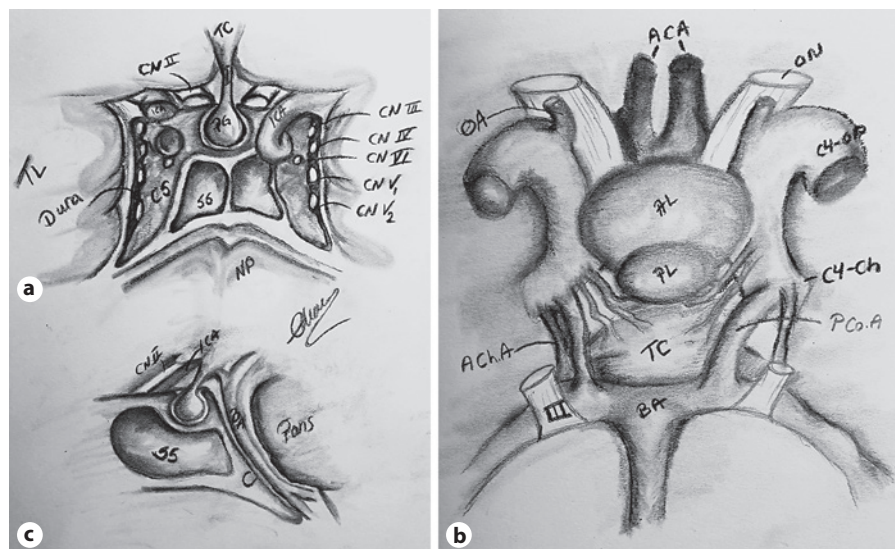
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## Introduction

The parasellar region is an anatomically complex area bordering the sella turcica and containing crossroads of many vital structures. The broad landscape of neoplastic lesions in the parasellar region is determined by the presence of numerous and histologically heterogeneous structures, as well as of embryonic remnants. With the exception of craniopharyngioma which very rarely arises outside this region, all other parasellar tumours can occur elsewhere, within or outside the central nervous system (CNS).

**Fig. 1.** Anatomical relationships. **a** Coronal section of the parasellar region. PG, pituitary gland; ICA, internal carotid artery; SS, sphenoid sinus; CS, cavernous sinus; CN, cranial nerve; V1, ophthalmic branch; V2, maxillary branch; NP, nasopharynx; TL, temporal lobe; I, infundibulum. **b** Inferior view. ACA, anterior cerebral artery; ON, optic nerve; OA, ophthalmic artery; C4-OP, cavernous segment of carotid artery, the ophthalmic part; AL, anterior lobe of the pituitary; PL, posterior lobe of the pituitary; TC, tuber cinereum; ACh.A, anterior choroidal artery; PCo. A, posterior communicating artery. **c** Sagittal section of the parasellar region. BA, basilar artery; C, clivus. Figure 1 is authored by Dr. Elham Roshtami.



In surgical series, the most frequent neoplasms in the parasellar region are invasive pituitary neuroendocrine tumours. All other neoplasms are rare and comprise about 9% of the tumours of different cell origin and histological malignancy grade [1, 2]. Metastases are uncommon but can occur even a long time after the diagnosis of the primary tumour and need to be included in the differential diagnosis [2, 3]. Originating from different cell types, the parasellar tumours are classified according to the World Health Organization (WHO) classification systems of different organs and tissues [4–7] (Table 1). Parasellar tumours can affect vital anatomical structures, causing a broad spectrum of manifestations, the type and severity of which depend on size, location, biological behaviour of the tumour and age at diagnosis [1, 8, 9]. These complex clinical aspects make the parasellar tumours challenging even when they have benign histological features. Surgery and/or radiotherapy of parasellar tumours can be associated with a high risk of acute and long-term endocrine, neurological, psychological and cognitive complications [2, 10, 11]. This necessitates the introduction of novel pharmacological therapies and definition of the predictive markers.

In this paper, we will summarise the literature covering histopathological and molecular genetic aspects of selected parasellar neoplasms. Given the limitations in the length of this mini review, we will focus on tumours occurring almost exclusively in the parasellar region, those showing a predisposition for the parasellar area and a few tumour types that have only rarely been described in this location. Despite their clinical significance, other lesions

usually covered in reviews describing central nervous and soft tissue tumours (e.g., meningiomas) will not be included. Recent advances in the diagnostics and rationales for novel pharmacological therapies will also be presented.

### Parasellar Region: Anatomical Considerations

The sellar region resides at the centre of the cranial base on the sphenoid bone with complex neural and vascular associations. The sella turcica (Turkish saddle) lies in the centre of the sphenoid bone containing the pituitary gland. Anteriorly is the tuberculum sellae and posteriorly the dorsum sellae and clivus. Inferior to the fossa is the sphenoid sinus. Below and behind the sella turcica is the sphenoid sinus that extends posteriorly to the clivus. Above, the sella is covered by the diaphragma sellae as a roof where the infundibulum of the pituitary gland passes through up to the hypothalamus (Fig. 1).

The parasellar region is a part of the middle fossa, between the sella and the temporal fossa. It can be defined as the area surrounding the sella turcica and includes suprasellar cistern, cavernous sinuses, hypothalamus and anterior inferior part of the third ventricle.

The suprasellar cistern is a cerebrospinal fluid-filled space shaped like a pentagon when viewed from above containing the circle of Willis. The infundibulum passes in the centre surrounded anteriorly by the optic chiasm and laterally by the uncus of the temporal lobes.

Cavernous sinuses lie lateral to the pituitary gland where the lateral part of the body of the sphenoid forms

**Table 1.** Types of parasellar tumours

Tissue of the origin	Tumour type
Embryonic remnants of Rathke's pouch*	Craniopharyngioma* – Adamantinomatous – Papillary
Notochordal remnants*	Notochordal tumours* – Benign notochordal cell tumour* – Chordoma* ○ Chordoma NOS ○ Chondroid chordoma ○ Dedifferentiated chordoma
Neural crest remnants*	Paranglioma*
Fibroblastic cell*	Solitary fibrous tumour/haemangiopericytoma*
Fibroblast/monocyte/osteoclast*	Giant cell tumour of the bone*
Germ cells*	Germinoma* Yolk sac tumour* Embryonal cell carcinoma* Choriocarcinoma* Teratoma* Mixed germ cell tumour*
Lymphocytic neoplasms*	Diffuse large B-cell lymphoma of the CNS*
Histiocytic neoplasms*	Langerhans cell histiocytosis* Disseminated juvenile xanthogranuloma* Erdheim-Chester disease*
Arachnoidea	Meningioma Grade I – Meningothelial – Fibrous – Transitional – Other histological types Grade II – Atypical – Chordoid – Clear cell Grade III – Anaplastic – Rhabdoid – Papillary
Chondroid tissue	Chondroma Chondrosarcoma
Bone	Osteoma Osteosarcoma
Adipose tissue	Lipoma Liposarcoma
Smooth muscle	Leiomyoma Leiomyosarcoma
Striated muscle	Rhabdomyosarcoma
Glia*	Pilocytic astrocytoma* Pilomyxoid astrocytoma* Chordoid glioma of the third ventricle*
Endothelium	Haemangioma
Unknown	Atypical teratoid/rhabdoid tumour
Schwann cells	Schwannoma Malignant peripheral nerve sheath tumour

\* Selected tumour types covered by the review. NOS, not otherwise specified; CNS, central nervous system.

the inferior part of the medial wall of the cavernous sinus, extending from the petrous apex to the superior orbital fissure.

The cavernous sinus is encapsulated by two layers of the dura. The oculomotor nerve (cranial nerve, CN III), trochlear nerve (CN IV), ophthalmic ( $V_1$ ) and maxillary ( $V_2$ ) branches of the trigeminal nerve (CN V) pass through the later wall of the cavernous sinus while the abducens nerve (CN VI) and carotid artery pass through the cavernous sinus.

The parasellar area is considered to be the smallest area of the skull base with the highest concentration of important neural and vascular structures making any neoplasm in this area potentially leading to the neurological deficits with life-threatening complications [12, 13].

### Craniopharyngioma

Craniopharyngioma is a histologically benign, although invasively growing, cystic and/or solid tumour originating from the embryonic remnants of Rathke's pouch [4]. This origin was proposed at the beginning of the 20th century based on the histological similarities between Rathke's pouch and craniopharyngiomas [14]. This hypothesis has been further supported by the recent identification of molecular markers of Rathke's pouch precursors in murine and human craniopharyngiomas [15, 16]. Craniopharyngiomas are almost exclusively located in the sellar and suprasellar regions [17]. The cerebellopontine angle is the most frequent location among uncommon cases of extrasellar craniopharyngiomas [18].

Craniopharyngioma occurs in two morphologically distinct variants. Adamantinomatous craniopharyngioma (ACP) is composed of squamous epithelium with focally looser "stellate reticulum," palisading of the basal cells and accumulation of degenerative, "wet keratin" [4] (Fig. 2a). Papillary craniopharyngioma (PCP) consists of non-keratinising squamous epithelium covering papillary fibrovascular cores [4] (Fig. 2d). Rarely, ACP and PCP coexist in the same lesion [19, 20]. ACP is the predominant subtype in childhood onset disease but may develop at all ages, whereas PCP is almost exclusively found in adults [4]. Craniopharyngioma has a distinct microscopic morphology. Differential diagnostic difficulties associated with other epithelial tumours (e.g., metastases) that can be rarely encountered in cases with sparse pathological material, are usually resolved by a multidisciplinary approach correlating histopathology, MRI find-

ings and clinical characteristics, such as patient age or history of malignancy in other organs.

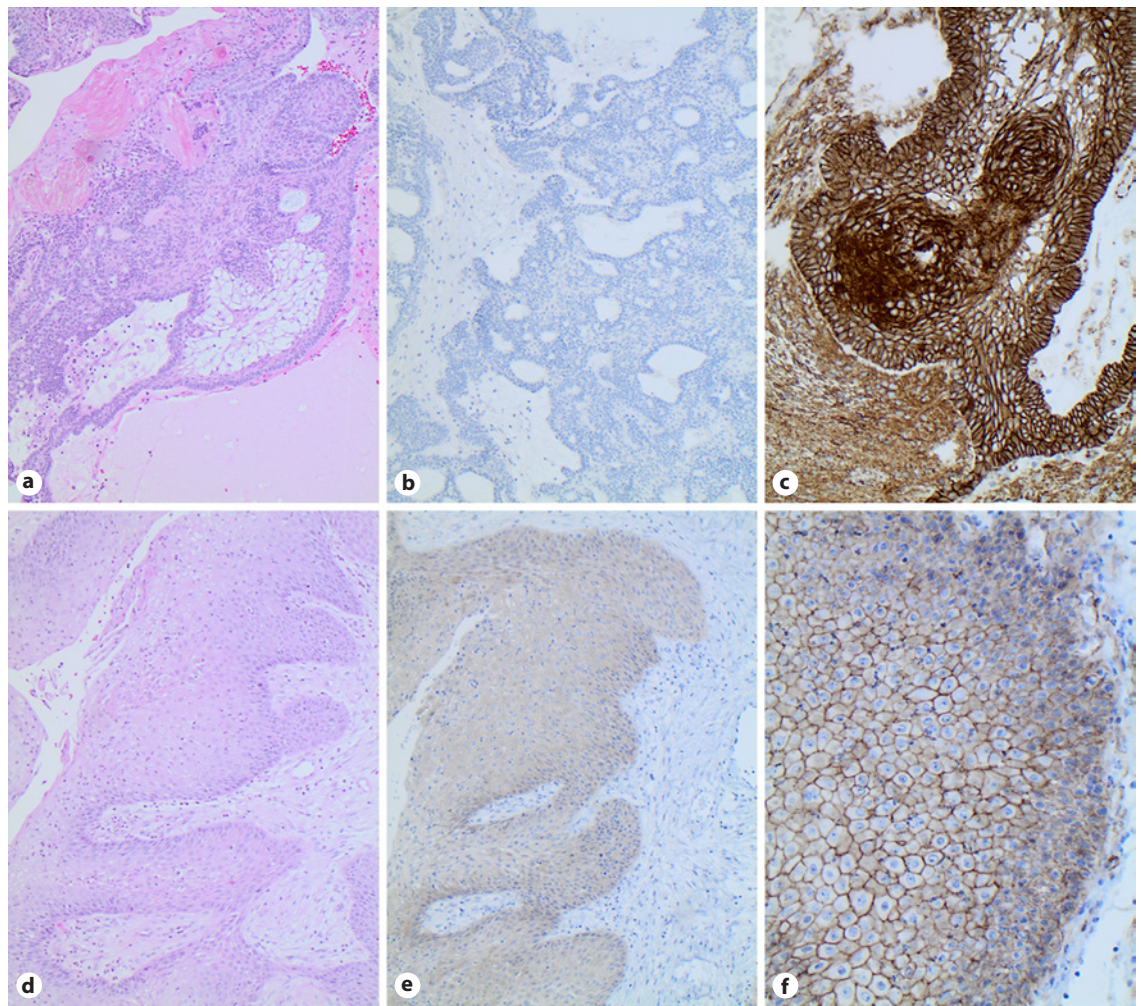
The molecular mechanisms behind the two histological variants of craniopharyngiomas have recently been clarified. ACP is characterised by mutations in the *CTNNB1* gene, encoding  $\beta$ -catenin, which subsequently lead to aberrant nuclear translocation of this protein as demonstrated by immunohistochemistry in a subset of tumour cells forming epithelial whorls [21] (Fig. 2c). Nearly all PCPs are driven by a *BRAFV600E* mutation that constitutively activates the MAPK/ERK signalling pathway [22]. Mutated *BRAFV600E* is expressed in epithelial neoplastic cells and can be demonstrated by using a monoclonal VE1 antibody (Fig. 2e) [23]. However, positive immunolabelling with the VE1 antibody without detectable *BRAFV600E* mutation has been demonstrated in the anterior pituitary gland, other endocrine organs and a subset of pituitary neuroendocrine tumours [24, 25]. Therefore, confirmation of the mutation by genetic analysis is recommended, particularly in patients who are candidates for BRAF-targeting therapy.

*BRAFV600E* inhibitors alone or in combination with MAPK/ERK inhibitors have been successfully used recently in PCPs [26–31]. On the other hand, drugs targeting  $\beta$ -catenin and its downstream MAPK pathway have been used only in in vitro studies, and their value in the management of ACP requires assessment in a clinical trial [32, 33]. Recently, the programmed cell death protein 1 and programmed cell ligand-1 (PD-1/PD-L1) have been demonstrated in epithelial neoplastic cells and immune cells of both ACP and PCP [34, 35] opening a new possible avenue for immune-mediating therapy of craniopharyngiomas.

### Chordoma

Chordomas are malignant tumours arising from the embryonic notochordal remnants typically affecting the most extreme part of the axial skeleton, clivus and lumbosacral vertebral column. They are surgically challenging to remove and may metastasise in up to 40% of cases, more commonly the spinal than the skull base chordomas [7]. Chordomas are composed of large, vacuolated "physaliphorous cells" frequently growing in a trabecular pattern surrounded by a myxoid matrix (Fig. 3a, b) [7]. Similar to the embryonic notochord, the neoplastic cells of chordoma express both epithelial (cytokeratin) and neuronal (S-100 protein) markers, as well as brachyury, a T-gene encoded transcription factor that plays a pivotal role





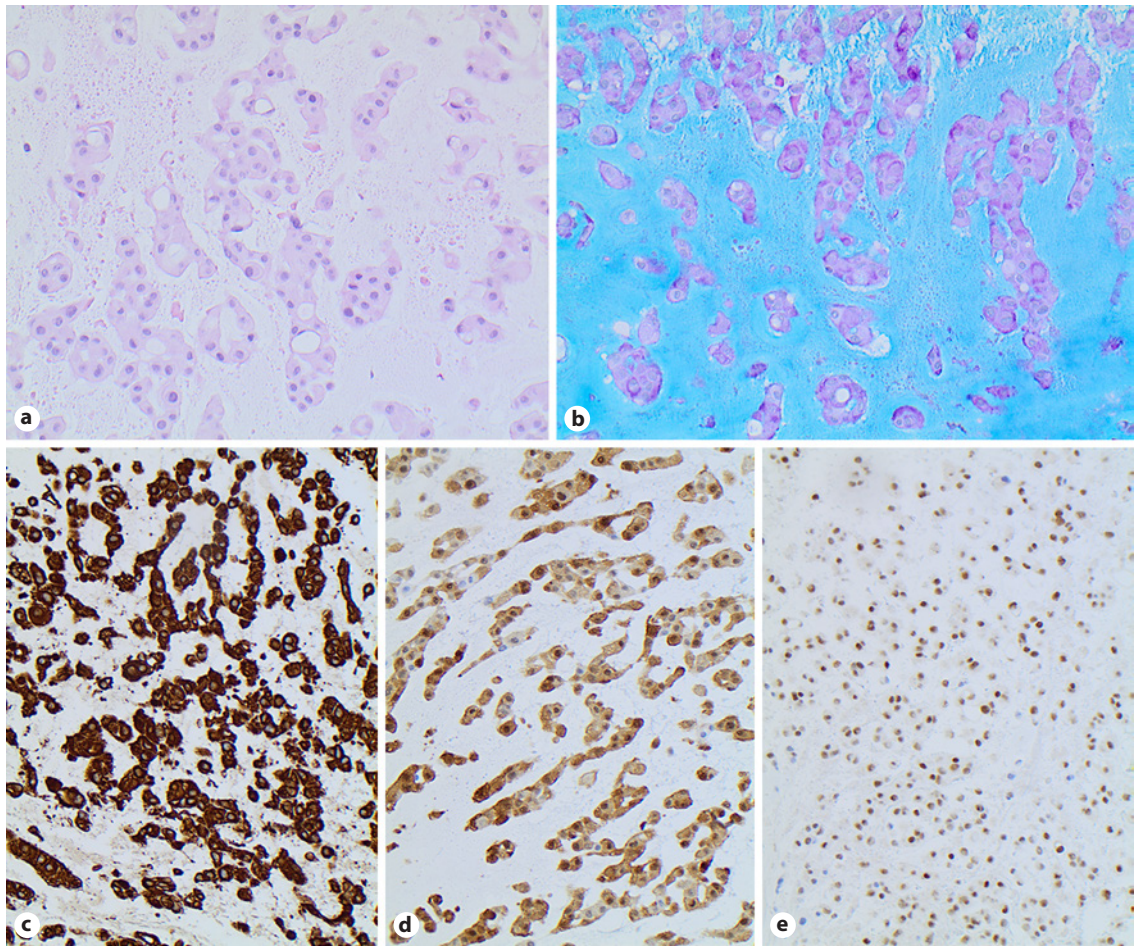
**Fig. 2.** Craniopharyngioma. Adamantinomatous type (upper row) characterised by: typical epithelial features with “wet keratin” and “stellate reticulum” (**a**, HE,  $\times 100$ ); lack of BRAFV600E immunolabelling (**b**,  $\times 100$ ); a nuclear translocation of  $\beta$ -catenin in tumour cells forming epithelial whorls (**c**,  $\times 200$ ). Papillary craniopharyngioma (lower row) characterised by: papillary projections of non-keratinising squamous epithelium (**d**, HE,  $\times 100$ ); expression of BRAFV600E (**e**,  $\times 100$ ) and membranous  $\beta$ -catenin positivity (**f**,  $\times 200$ ).

in the notochord differentiation (Fig. 3c–e) [36, 37]. Although rarely expressed in other tumours, brachyury is a specific marker valuable in the pathological differentiation of chordoma from chondroma, chondrosarcoma, chordoid meningioma and carcinomas [38]. Germ-line duplications of T gene encoding brachyury are associated with familial predisposition to chordoma [39].

Apart from the most frequent conventional chordoma or chordoma not otherwise specified, the WHO classification defines two additional rare subtypes [7], the chondroid chordoma and the dedifferentiated chordoma. In chondroid chordoma, the myxoid matrix resembles hyaline cartilaginous tumour. This subtype has no prognos-

tic value but needs to be discriminated from chondroma and chondrosarcoma based on morphology, brachyury expression in chordoma and evidence of isocitrate dehydrogenase 1 or 2 (*IDH1/2*) mutations in a subset of chondromas and chondrosarcomas [40]. Dedifferentiated chordoma is a biphasic tumour with a conventional brachyury-positive chordoma component and a dedifferentiated, spindle cell sarcoma component which has loss of brachyury [7]. In 5 out of 6 recently reviewed cases, this high-grade malignant subtype developed through dedifferentiation secondary to radiotherapy or after incomplete surgical removal of a conventional chordoma [41]. Not included in the current WHO classification is a rare





**Fig. 3.** Chordoma not otherwise specified demonstrating “physaliphorous” tumour cells arranged in trabecules (a, HE, ×200), rich myxoid matrix surrounding the tumour cells (b, Alcian blue/PAS, ×200), cytokeratin AE1/AE3 (c, ×200), S-100 (d, ×200) and nuclear brachyury expression (e, ×200).

paediatric poorly differentiated chordoma of the clivus characterised by loss of SMARCB1 (INI1) and poor prognosis [42, 43]. Brachyury expression is valuable to differentiate this variant from INI1-negative atypical teratoid rhabdoid tumour that has exceptionally been reported in the sellar region [42, 44–46].

Benign notochordal cell tumour has a very indolent course and should not be misdiagnosed as a chordoma. It is composed of adipocyte-like, brachyury-positive cells and lacks a myxoid matrix. Despite occasional coexistence in the same lesion, there is no evidence that benign notochordal cell tumour is a precursor of chordoma [7, 47–49].

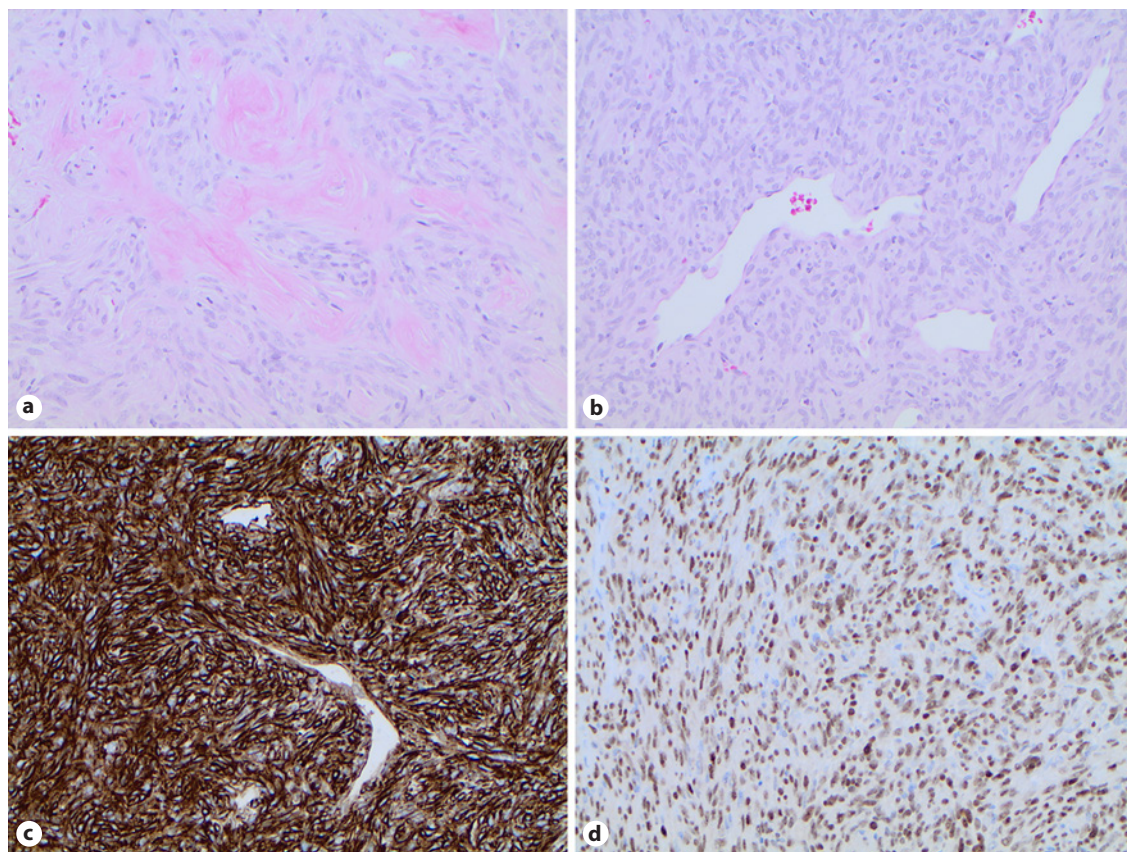
Mutations in the PI3K/AKT/TSC1/TSC2/mTOR signalling pathway in chordomas could be potential targets of mTOR inhibitors [50]. Nonetheless, current data suggest suboptimal response to these agents [51]. Furthermore, initial results with immune-check point inhibitors

and brachyury-targeting therapy have not been encouraging [52]. Tazemetostat, an inhibitor of EZH2 protein which is upregulated in tumours characterised by SMARCB1 loss, is under a clinical trial and has shown promising results in paediatric patients with poorly differentiated chordomas [51].

### Paraganglioma

Paragangliomas are neuroendocrine neoplasms, usually encapsulated and benign. It is postulated that they arise from remnant neural crest cells which are diffusely dispersed or are associated with segmental or collateral autonomic ganglia (paraganglia). In the CNS, paragangliomas primarily affect the cauda equina/filum terminale and jugulotympanic regions [4]. Less than 20 cases





**Fig. 4.** Haemangiopericytoma/solitary fibrous tumour. **a** Solitary fibrous tumour phenotype characterised by spindle cells arranged in fascicles separated by thick collagenous bands. HE,  $\times 200$ . **b** Haemangiopericytoma phenotype with haphazard growth pattern of cells with round to ovoid nuclei and thin-walled branching vessels. HE,  $\times 200$ . **c, d** CD34 expression (**c**,  $\times 200$ ) and nuclear expression of STAT6 (**d**,  $\times 200$ ).

of primary sellar/parasellar paraganglioma have been reported and recently reviewed; none of them had evidence of catecholamine secretion [53, 54].

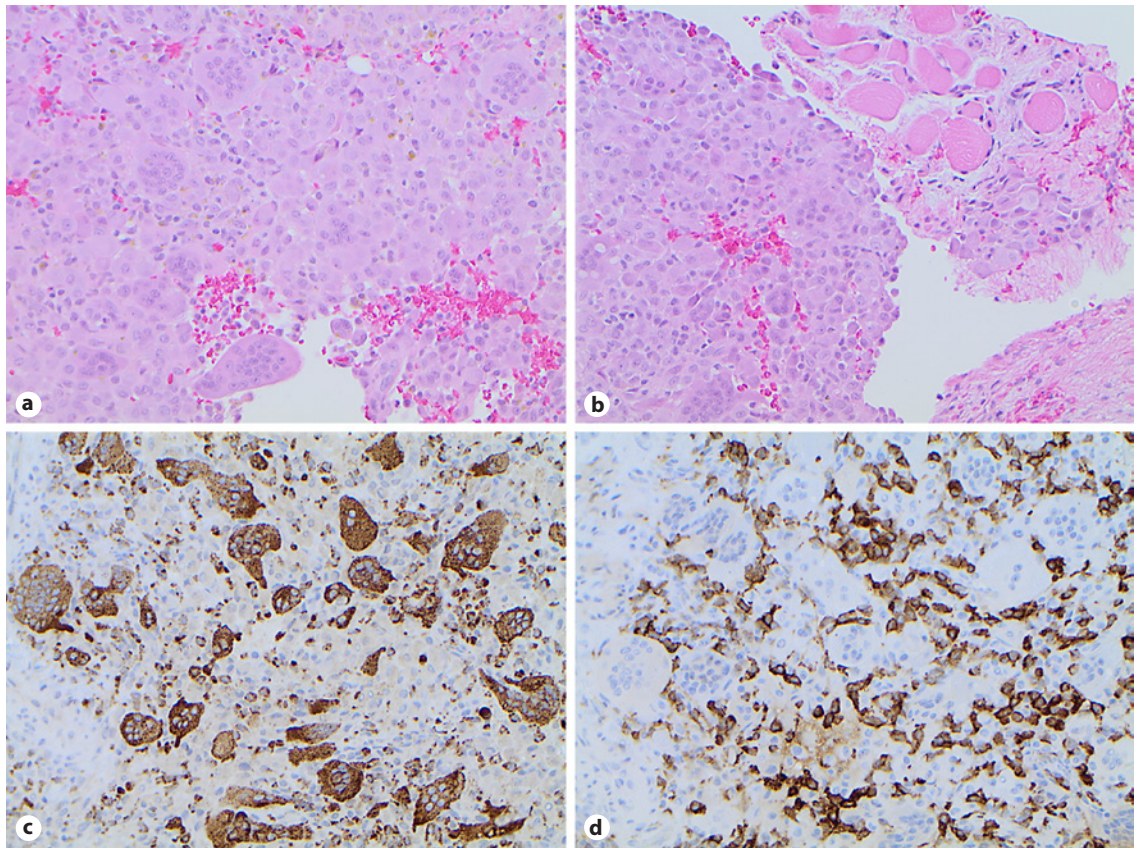
Although classified as histologically benign WHO grade I tumours, paragangliomas may demonstrate invasive growth and in up to 20% of cases, there are even distant metastases [4]. Distant metastases have not been reported as yet in parasellar paragangliomas [53]. Genetic analysis for identifying familial cases is needed, and its results will determine further monitoring.

Histologically, paragangliomas are composed of synaptophysin- and chromogranin A-positive neuroendocrine chief cells that form a typical lobular, “zellballen” pattern emphasised by peripheral S-100- and glial fibrillary acidic protein-immunolabelled sustentacular cells. Expression of cytokeratin may vary and be absent in primary sellar paragangliomas [53]. Mitotic figures and necrosis are rare [4]. There are no histological parameters reliably predicting the risk for invasive growth or meta-

static potential. In cases without typical morphology, positive immunolabelling for tyrosine hydroxylase and lack of organ-specific transcription factors can be helpful to differentiate paraganglioma from pituitary neuroendocrine tumours or metastases of neuroendocrine tumours from other locations.

Up to 50% of adult paragangliomas and more than 80% of paediatric ones are associated with germline mutations [4], most frequently in one of the succinate dehydrogenase (SDH) genes: *SDHA*, *SDHB*, *SDHC*, *SDHD*, *SDHAF2* [55–59]. In addition to family history, early onset, multiple tumour occurrence and association with non-paraganglial tumours should raise suspicion for genetic predisposition [60]. Immunohistochemistry on sections from formalin-fixed paraffin-embedded tissue is a reliable method to detect SDHx mutations [61, 62], with loss of SDHB revealing mutations in different *SDH* genes [61]. Recently, somatic *ATRX* mutations, which can be suspected on the basis of the lack of *ATRX* in the tumour





**Fig. 5.** Giant cell tumour of the bone. **a** Neoplastic mononuclear cells admixed with macrophages and osteoclast-like giant cells. HE, ×200. **b** Tumour cells infiltrating extracranial muscle. HE, ×200. **c** CD68-positive reactive cells. ×400. **d** CD163 immunolabelling of neoplastic cells. ×400.

cells, have been reported and strongly associated with a risk for metastatic paragangliomas [63, 64]. Somatic mutations in isocitrate dehydrogenase are extremely uncommon in paragangliomas [65] and can coexist with *ATRX* mutations [66].

### Haemangiopericytoma/Solitary Fibrous Tumour

Haemangiopericytoma is a mesenchymal tumour of fibroblastic type. It represents a histological spectrum of neoplasms previously classified separately as meningeal solitary fibrous tumour (SFT) and haemangiopericytoma (HPC) [4]. In the CNS, HPC and SFT are usually, but not always, connected to the cranial or spinal dura [67]. The sellar/parasellar region is an uncommon location with less than 20 cases reported until now in sporadic case reports that are seldomly comprehensively reviewed [68].

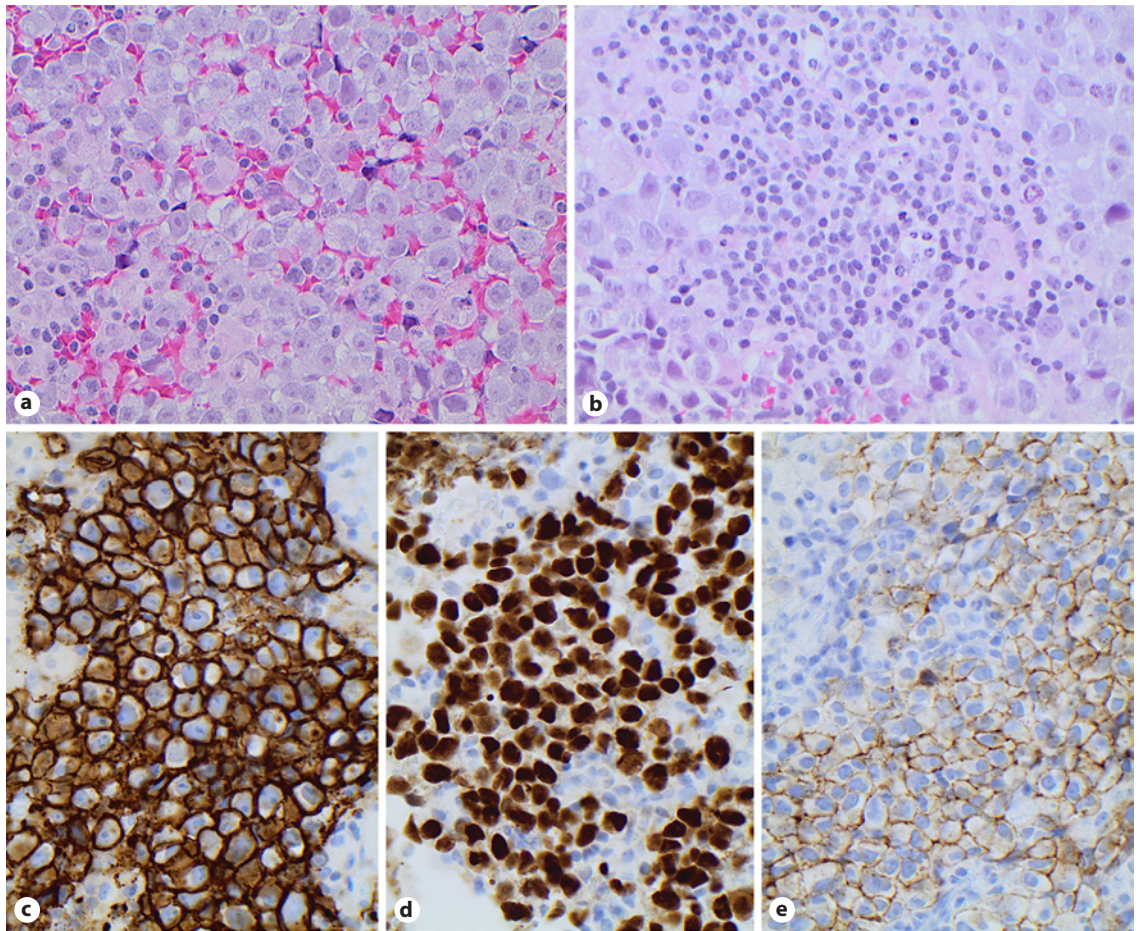
A distinct molecular feature unifying SFT and HPC into one group is a fusion of *NAB2* and *STAT6* genes [4,

69, 70] which results in nuclear translocation of STAT6 protein; this can be detected by immunohistochemistry and represents a key diagnostic feature of SFT/HPC [71]. Nuclear STAT6 expression is also a useful marker for the differential diagnosis towards fibrous meningioma or sellar schwannoma that can be particularly challenging when the surgical material is sparse and the morphology not typical.

Morphologically, SFTs are tumours composed of spindle cells growing in fascicles separated by thick collagenous bands. HPCs are characterised by haphazard arrangement of cells with spindle-shaped to oval nuclei surrounded by a rich and delicate reticulin network and characteristic staghorn vascular pattern. Both morphological types, besides nuclear STAT6 positivity, express typically vimentin and CD34 (Fig. 4) [4]. Several studies indicate that the morphological phenotype depends on the type of *NAB2/STAT6* fusion [72–75].

SFT is a benign WHO grade I tumour, whereas the HPC phenotype demonstrates more aggressive behav-





**Fig. 6.** Germinoma characterised by: sheets of uniform rounded cells with clear cytoplasm (**a**, HE, ×400); focal lymphocytic infiltration (**b**, HE, ×400); membranous D2-40 expression (**c**, ×400); nuclear Oct 3/4 (**d**, ×400) and membranous CD117 (**e**, ×400) immunolabelling.

ious with a relatively high rate of recurrence and risk of metastasis giving ground to its higher malignancy grade compared to the SFT. The single histological criterion to differentiate between WHO grade II and grade III HPC is the mitotic count with a cut-off level of 5 mitoses per 10 high-power field [4]. In a recent study, a three-tiered system including both mitotic count and necrosis seemed to provide the most accurate prognostic stratification within this tumour family [75].

### Giant Cell Tumour of Bone

Giant cell tumour (GCT) of bone is a benign but locally aggressive primary bone neoplasm that typically affects the epiphyses of long bones. In uncommon cases of skull involvement, GCT shows a predilection for tempo-

ral and sphenoid bone [76]. Rare primary malignancies and malignancy secondary to radiotherapy in GCT [77, 78] could be, at least partially, explained by p53 mutations [79, 80].

Histologically, the GCT is composed of a proliferation of neoplastic mononuclear cells admixed with numerous macrophages and large reactive osteoclast-like giant cells. The neoplastic cells express CD163, a macrophage and monocyte activation marker, and lack CD68, a classical macrophage marker expressed in reactive macrophages and osteoclast-like giant cells of the GCT [7] (Fig. 5). More than 90% of GCTs are characterised by a distinct H3.3 histone mutation in *H3F3A* [81] which is used for the differentiation from the other giant cell, osteoclast-rich bone tumours and chondroblastomas, especially in scarce fine-needle biopsy specimens [82, 83]. Due to decalcification protocols applied to the bone tumour speci-

mens, molecular pyrosequencing-based techniques seem to be more reliable than immunohistochemistry in the identification of *H3F3A* mutations [84].

## Germ Cell Tumours

Intracranial germ cell tumours arise along the cranial midline axis, slightly less frequently in the suprasellar than in the pineal region, with predilection for children and young adult males [4]. Simultaneous occurrence of suprasellar and pineal germ cell tumour has been designated as “bifocal germ cell tumour” [85]. The germ cell tumours, except benign teratomas, are malignant and can easily metastasise through the cerebrospinal fluid, e.g. “drop metastases.” In the CNS, germ cell tumours represent the morphological, immunophenotypic and genetic homologues of gonadal and other extraneuraxial germ cell neoplasms [4]. The histogenesis of these tumours in the CNS is unclear. An origin from the primordial germ cells remaining in the neuraxial midline due to aberrant migration to the gonadal ridges or from the native neural stem cells of embryonic pluripotent type has been suggested [86–89]. A significantly higher incidence in eastern Asia which persists even in ancestries settled in the other parts of the world suggests the implication of genetic factors [4, 90].

The WHO classification system recognises 5 histological types of germ cell tumours: germinomas, embryonal carcinoma, yolk-sac tumour, choriocarcinoma and teratoma. Mixed types with the presence of different tumour components are not uncommon [4]. Germ cell tumours can be divided into two risk groups: germinomas and non-germinomas, with significantly better prognosis after radio- and chemotherapy for the former group [91]. The most frequent subtype, germinoma is characterised by sheets of rounded CD117, D2-40, OCT4 and NANOG-positive cells surrounded by lymphocytes, dominantly of T-cell phenotype (Fig. 6). Lymphocytic infiltration, sometimes with formation of germinal centres, can mask the typical morphology and represent a challenging differential diagnosis versus chronic inflammatory lesion or haematological malignancies, especially in scarce specimens. In such cases, a detailed clinical, radiological and pathological correlation is highly recommended. Other histological subtypes are very rare in the CNS as a primary location and show the histological pattern seen in the gonadal presentation.

Recent molecular investigations of germ cell tumours revealed mutations in the MAPK pathway frequently as-

sociated with male gender [91]. Recurrent mutations in the mTOR pathway in intracranial germ cell tumours have emerged as potential therapeutic targets [92]. Rich lymphocytic infiltration in germinomas and expression of PD-1 and PDL-1 on the inflammatory cells within germinomas may potentially be targeted by immune check point inhibitors [93].

## Haematopoietic and Lymphoid Tumours

Even though lymphomas and histiocytic cell neoplasms are rarely observed in the CNS, as a solitary lesion or in the form of the disseminated disease, the parasellar region could also be affected.

Similarly, to the CNS lymphomas in general, rare parasellar lymphomas belong to diffuse large B-cell lymphomas [94].

Several types of histiocytic disorders, such as Langerhans cell histiocytosis, disseminated juvenile xanthogranuloma and Erdheim-Chester disease, may have predilection for the parasellar region. Morphological, immunohistochemical and molecular genetic features of these tumours are in detail presented elsewhere [6]. Although considered as reactive in the past, the majority of histiocytic lesions in the CNS including the parasellar region represent true monoclonal neoplasms [6] that need to be differentiated from the secondary inflammatory lesions [95].

## Glial Tumours

Even though glial tumours of all types could be localised in the parasellar space, pilocytic astrocytoma, pilomyxoid astrocytoma and chordoid glioma of the third ventricle show predilection for this region [4]. These can be differentiated from other tumour types based on their morphology and on the expression of glial fibrillary acidic protein that confirms the glial origin of the tumour cells.

The optic tract and hypothalamus comprise preferable supratentorial location for pilocytic astrocytoma. Pilocytic astrocytoma involving the optic nerve is a hallmark of neurofibromatosis type 1 [4]. A majority of pilocytic astrocytomas contain a *KIAA1549-BRAF* fusion gene [96]. *BRAFV600E* mutation is, however, associated with extracerebellar tumour location in a subset of patients [97]. Although in general slowly growing tumours corresponding to WHO grade 1, pilocytic astrocytomas in parasellar



location may not be amenable to gross total resection, which increases a risk of recurrence and progress [4].

Pilomyxoid astrocytoma is a variant of pilocytic astrocytoma of uncertain malignancy grade preferentially affecting the hypothalamic/chiasmatic region in young children [4].

Chordoid glioma of the third ventricle is a rare, WHO grade II neoplasm of adult patients with favourable prognosis when totally resected [4]. However, the tumour is mostly attached or invades the hypothalamus; consequently, only subtotal resection has been reported. A recent study defined *PRKCA* mutation as a recurrently mutated oncogene in pilomyxoid astrocytoma, which may have potential therapeutic implications [98].

## Conclusion

A wide heterogeneity of parasellar neoplasms demands a huge experience in neuropathology in order to cover this fascinating field and avoid pitfalls in histopath-

ological diagnostics. Integration of the molecular genetic mechanisms in the evolving WHO tumour classification increases diagnostic accuracy and enables new targeted pharmacotherapies giving hope for an optimised impact on the patients' prognosis and outcome. A multidisciplinary approach is required in order to overcome challenges in the diagnostics and treatment of patients with parasellar neoplasms.

## Disclosure Statement

The authors have no conflicts of interest to declare.

## Author Contributions

Olivera Casar-Borota recommended the structure of the paper and prepared the final version. Emilija Manojlovic-Gacic wrote the first draft. Elham Rostami contributed with the anatomy section, Figure 1 and clinical comments. Niki Karavitaki contributed with clinical comments and discussions. All the authors read, edited and approved the final paper.

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